

In the Claims:

Please cancel claims 3-8 and 18 without prejudice to the inclusion of the subject matter contained therein in any later filed continuation and/or divisional application(s).

Please amend claims 1, 2, 16, 17, 19, 20-25, 27 and 37 as follows:

1. (Currently Amended) An isolated nucleic acid molecule encoding a Tumor Necrosis Factor (TNF)-Related Activation Induced Cytokine (TRANCE) polypeptide, wherein the amino acid sequence of said TRANCE polypeptide consists of the amino acid sequence as set forth in Figure 2 (SEQ ID NO:2)~~comprising the DNA sequence set forth in Figure 1 (SEQ ID NO:1) or degenerate variants thereof, or fragments thereof.~~

2. (Currently Amended) An isolated nucleic acid molecule encoding a TRANCE polypeptide, wherein the nucleotide sequence of said isolated nucleic acid molecule consists of the sequence as set forth in SEQ ID NO:1~~or degenerate variants thereof, or fragments thereof, hybridizable to said DNA sequence of Claim 1 under standard hybridization conditions.~~

Claims 3-8. (Canceled)

9. (Withdrawn) An isolated polypeptide comprising the amino acid sequence of FIG. 2 (SEQ ID NO:2), conservative variants thereof, fragments thereof or analogs or derivatives thereof, or the amino acid sequence of FIG. 4 (SEQ ID NO:4), conservative variants thereof, or fragments thereof, or analogs or derivatives thereof.

10. (Withdrawn) An antibody having the polypeptide of claim 9 as an immunogen.

11. (Withdrawn) The antibody of claim 10, wherein said antibody is a monoclonal antibody.

12. (Withdrawn) The antibody of claim 10, wherein said antibody is a polyclonal antibody.

13. (Withdrawn) The antibody of claim 10, wherein said antibody is a chimeric antibody.

14. (Withdrawn) The antibody of claim 10, wherein said antibody is detectably labeled.

15. (Withdrawn) The antibody of claim 14, wherein a detectable label comprises an enzyme, a radioactive isotope, or a chemical which fluoresces.

16. (Currently Amended) An expression vector comprising ~~the~~said isolated nucleic acid molecule of ~~claim~~Claim 1 operatively associated with a promoter.

17. (Currently Amended) An expression vector comprising ~~the~~said isolated nucleic acid molecule of ~~claim~~Claim 2 operatively associated with a promoter.

Claim 18. (Canceled)

19. (Currently Amended) The expression vector of ~~any of Claims~~claims 16 or 17[[16-18]], wherein said promoter is selected from the group consisting of the immediate early promoters of hCMV, early promoters of SV40, early promoters of adenovirus, early promoters of vaccinia, early promoters of polyoma, late promoters of SV40, late promoters of adenovirus, late promoters of vaccinia, late promoters of polyoma, the lac the trp system, the TAC system, the TRC system, the major operator and promoter regions of phage lambda, control regions ~~of~~of fd coat protein, 3-phosphoglycerate kinase promoter, acid phosphatase promoter, promoters of yeast α mating factor.

20. (Currently Amended) A unicellular host transformed with an expression vector ~~of any of claims~~Claims 16 or 17[[16-18]].

21. (Currently Amended) The unicellular host according to ~~claim~~Claim 20, wherein said host comprises E. coli, Pseudonomas, Bacillus, Strepomyces, yeast, CHO, R1.1, B-W, L-M, COS1, COS7, BSC1, BSC40, BMT10 or Sf9 cells.

22. (Currently Amended) A mammalian cell comprising a DNA sequence which encodes a TRANCE polypeptide, wherein the amino acid sequence of said TRANCE polypeptide consists of the amino acid sequence as set forth in Figure 2 (SEQ ID NO:2) TRANCE, and further wherein said mammalian cell is modified *in vitro* to permit higher expression of TRANCE by ~~means of a homologous recombinational event consisting of inserting a promoter in functional proximity to the TRANCE polypeptide encoding sequence.~~

23. (Currently Amended) ~~A~~The mammalian cell of claim~~according to Claim 22,~~ wherein the promoter is a TRANCE polypeptide promoter ~~and the homologous recombinational event replaces a mutant TRANCE polypeptide promoter.~~

24. (Currently Amended) A method of producing an isolated polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2), ~~conservative variants thereof, fragments thereof or analogs or derivatives thereof, or the amino acid sequence of Figure 4 (SEQ ID NO:4), conservative variants thereof, or fragments thereof, or analogs or derivatives thereof,~~ comprising the steps of:

a) culturing a unicellular host transformed with an expression vector comprising an isolated nucleic encoding a Tumor Necrosis Factor (TNF)-Related Activation Induced Cytokine (TRANCE) polypeptide, wherein the amino acid sequence of said TRANCE polypeptide consists of the amino acid sequence as set forth in Figure 2 (SEQ ID NO:2)~~of Claim 20~~ under conditions that provide for expression of said isolated polypeptide; and

b) recovering said isolated polypeptide from said host, the culture, or both.

25. (Currently Amended) A modulator of immune response in a mammal comprising:

a) ~~a polypeptide having an amino acid sequence set forth in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4) or conservative variants thereof, or a fragment thereof;~~

b) ~~an analog or derivative of a polypeptide having an amino acid set forth in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), or conservative variants thereof, or a fragment thereof;~~

~~e) a fusion protein comprising an amino acid sequence of Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), conservative variants thereof, or a fragment thereof;~~

~~d) an antibody having an immunogen selected from the group consisting of:~~

~~—— i) a polypeptide having an amino acid sequence set forth in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4) or conservative variants thereof, or a fragment thereof;~~

~~—— ii) an analog or derivative of a polypeptide having an amino acid as set forth in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), or conservative variants thereof, or a fragment thereof;~~

~~—— iii) a fusion protein wherein its amino acid sequence comprises an amino acid sequence of Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), conservative variants thereof, or a fragment thereof; or~~

d) an anti-sense TRANCE nucleic acid comprising at least one phosphodiester analog bond.

26. (Withdrawn) The modulator of claim 25, wherein said modulator is an agonist of TRANCE, and modulates immune response by increasing the life span of mature dendritic cells and increasing T cell activation, wherein said modulator comprises: a) a polypeptide having an amino acid sequence set forth in FIG. 2 (SEQ ID NO:2), FIG. 4 (SEQ ID NO:4) or conservative variants thereof, or a fragment thereof; b) an analog or derivative of a polypeptide having an amino acid as set forth in FIG. 2 (SEQ ID NO:2), FIG. 4 (SEQ ID NO:4), or conservative variants thereof, or a fragment thereof; or c) a fusion protein wherein its amino acid sequence comprises an amino acid sequence of FIG. 2 (SEQ ID NO:2), FIG. 4 (SEQ ID NO:4), conservative variants thereof or a fragment thereof.

27. (Currently Amended) ~~The~~A modulator of immune response in a mammal as ~~set forth in Claim 25~~, wherein said modulator is an antagonist of TRANCE and modulates immune response by decreasing the life span of mature dendritic cells and decreasing T cell activation, wherein said modulator comprises:

~~an antibody having an immunogen selected from the group consisting of:~~

~~—— i) a polypeptide having an amino acid sequence set forth in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4) or conservative variants thereof, or a fragment thereof;~~

~~—— ii) an analog or derivative of a polypeptide having an amino acid as set forth in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), or conservative variants thereof, or a fragment thereof; and~~

~~—— iii) a fusion protein comprising an amino acid sequence set forth in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), conservative variants thereof, or a fragment thereof; or~~
b) an anti-sense TRANCE nucleic acid comprising at least one phosphodiester analog bond.

28. (Withdrawn) A TRANCE agonist pharmaceutical composition comprising said modulator of claim 25 and a pharmaceutically acceptable carrier thereof.

29. (Withdrawn) A method for treating an immune system related condition in a mammal, said method comprising the steps of: a) exposing at least one mature dendritic cell of the mammal to an antigen so that the at least one mature dendritic cell can present the antigen on its surface; and b) administering to the mammal a therapeutically effective amount of a TRANCE agonist pharmaceutical composition of claim 27.

30. (Withdrawn) The method for treating an immune system related condition as set forth in claim 29, wherein said antigen is selected from the group consisting of: a) a pathogen, or a fragment thereof; b) a virus, or a fragment thereof; and c) a tumor, or a fragment thereof.

31. (Withdrawn) The method for treating an immune system related condition as set forth in claim 29, wherein the immune system related condition is HIV or cancer.

32. (Withdrawn) The method for treating an immune system related condition as set forth in claim 29, wherein said pharmaceutically composition is administered orally, pulmonarily, or nasally.

33. (Withdrawn) The method for treating an immune system related condition as set forth in claim 29, further comprising the steps of removing the at least one mature dendritic cell from the mammal prior to the exposing step, and reintroducing the mature dendritic cell into the mammal after the exposing step, and prior to the administering step.

34. (Withdrawn) The method for treating an immune system related condition as set forth in claim 33, wherein the antigen is selected from the group consisting of: a) a pathogen, or a fragment thereof; b) a virus, or a fragment thereof; and c) a tumor, or a fragment thereof.

35. (Withdrawn) The method for treating an immune system related condition as set forth in claim 33, wherein the immune system related condition is HIV or cancer.

36. (Withdrawn) The method for treating an immune system related condition as set forth in claim 29, wherein said pharmaceutical composition is administered orally, pulmonarily, or nasally.

37. (Currently Amended) A TRANCE ~~antagonist~~ pharmaceutical composition comprising ~~said modulator of Claim 25~~ an anti-sense TRANCE nucleic acid and a pharmaceutically acceptable carrier thereof.

38. (Withdrawn) A method for treating an immune system related condition in a mammal, comprising administering to the mammal a therapeutically effective amount of the TRANCE antagonist pharmaceutical composition of claim 37.

39. (Withdrawn) The method for treating an immune system related condition in a mammal as set forth in claim 38, wherein said condition is related to over-expression of TRANCE protein in the mammal.

40. (Withdrawn) The method for treating an immune system related condition in a mammal as set forth in claim 39, wherein said condition is an autoimmune disease or hypersensitivity to an allergen.

41. (Withdrawn) A method for modulating levels of expression of a TRANCE protein in a mammal, comprising the steps of: a) removing at least one hematopoietic stem cell from the mammal; b) destroying remaining hematopoietic stem cells in the mammal; c) transfecting the at least one hematopoietic stem cell with a vector comprising an isolated nucleic

acid molecule which encodes a TRANCE protein such that the nucleic acid molecule becomes incorporated into the genome of the hematopoietic stem cell, forming a transfected hematopoietic stem cell; and d) introducing the transfected hematopoietic stem into the mammal so that the transfected hematopoietic stem cell can self replicate and differentiate within the mammal.

42. (Withdrawn) The method for modifying levels of expression of a TRANCE protein in a mammal as set forth in claim 41, wherein the nucleic acid molecule has a DNA sequence as set forth in FIG. 1 (SEQ ID NO:1) or degenerate variants thereof.

43. (Withdrawn) A method of diagnosing an immune system related condition in a mammal, wherein the method comprises the steps of: a) removing a bodily sample from the mammal; and b) assaying the bodily sample to determine whether TRANCE is expressed in the bodily sample.

44. (Withdrawn) The method of diagnosing an immune system related condition in a mammal as set forth in claim 43, wherein the mammal is a human.

45. (Withdrawn) The method of diagnosing an immune system related condition as set forth in claim 44, wherein the TRANCE protein is encoded by a nucleic acid molecule having a DNA sequence as set forth in FIG. 1 (SEQ ID NO:1), or degenerate variants thereof.

46. (Withdrawn) The method of diagnosing an immune system related condition as set forth in claim 44, wherein TRANCE has an amino acid sequence as set forth in FIG. 2 (SEQ ID NO:2), or conservative variants thereof.

47. (Withdrawn) The method of diagnosing an immune system related condition of claim 43, wherein the bodily sample is blood or lymphoid tissue.

48. (Withdrawn) The method of diagnosing an immune system related condition of claim 43, wherein the step of assaying the bodily sample to determine whether TRANCE is expressed in the bodily sample comprising contacting the bodily sample to an antibody to

TRANCE, and detecting the binding of the antibody to TRANCE.

49. (Withdrawn) The method of diagnosing an immune system related condition of claim 43, wherein the step of assaying the bodily sample to determine whether TRANCE is expressed in the bodily sample comprising contacting the bodily sample to an isolated nucleic acid molecule hybridizable under standard hybridizations to an isolated nucleic acid molecule comprising the DNA sequence of SEQ ID NO:1, and detecting the hybridization of said nucleic acid molecules.

50. (Withdrawn) The method of diagnosing an immune system related condition of claim 43, wherein said lymphoid tissue is selected from the group consisting of lymph node tissue, spleen tissue, and thymus tissue.

51. (Withdrawn) The method of diagnosing an immune system related condition of claim 43, wherein the immune system related condition is an autoimmune disease.

52. (Withdrawn) A method for modulating immune response to an antigen in an animal, comprising the steps of: a) removing an immature dendritic cell from the animal; b) pulsing the immature dendritic cell from the animal with the antigen ex vivo, so that immature dendritic cells present the antigen on their surface; b) inducing maturation of immature dendritic cells ex vivo; c) pulsing the mature dendritic cells with a modulator of immune response ex vivo; d) introducing the mature dendritic cells into the animal.

53. (Withdrawn) The method of claim 52, wherein the step of interacting immature dendritic cells with the antigen ex vivo comprises: a) transfecting immature dendritic cells with an expression vector comprising a nucleic acid molecule which encodes the antigen, operatively associated with a promoter; and b) inducing expression of the nucleic acid.

54. (Withdrawn) The method for modulating immune response of claim 52, wherein the immature dendritic cells comprise bone marrow derived immature dendritic cells.

54. (Withdrawn) The method of claim 52, wherein the antigen comprises: a) a

pathogen, or a fragment thereof; b) a virus, or a fragment thereof, c) a tumor, or a fragment thereof.

56. (Withdrawn) A method for increasing the viability of a dendritic cell, comprising contacting the dendritic cell with an isolated TRANCE comprising an amino acid sequence of SEQ ID NO:2, conservative variants thereof, fragments thereof, or analogs or derivatives thereof, wherein said dendritic cell is contacted by said isolated TRANCE has an increased viability relative to control dendritic cell not contacted with said isolated TRANCE.

57. (Withdrawn) The method of claim 56, wherein the contacting of the dendritic cell with said isolated TRANCE occurs in vitro or in vivo.

58. (Withdrawn) A method of increasing viability of a dendritic cell, comprising contacting the dendritic cell with an isolated TRANCE comprising an amino acid sequence of SEQ ID NO:4, conservative variants thereof fragments thereof, or analogs or derivatives thereof, wherein said dendritic cell contacted by isolated TRANCE has an increased viability relative to a control dendritic cell not contacted with said isolated TRANCE.

59. (Withdrawn) The method of claim 58, wherein the contacting of the dendritic cell with the isolated TRANCE occurs in vitro or in vivo.

60. (Withdrawn) A method of increasing viability of a dendritic cell, comprising contacting the dendritic cells with an isolated TRANCE comprising an amino acid sequence of SEQ ID NO:2, conservative variants thereof, fragments thereof, or analogs or derivatives thereof, and contacting the dendritic cell with an isolated protein which is a member of the Tumor Necrosis Factor (TNF) superfamily of proteins, such that the dendritic cell comprises an increased viability relative to a control dendritic cell not pulsed with TRANCE and the protein.

61. (Withdrawn) The method of claim 60, wherein the contacting steps occur simultaneously.

62. (Withdrawn) The method of claim 60, wherein the isolated protein which is a

member of the TNF superfamily comprises CD40L or TNF- α .

63. (Withdrawn) A method of increasing viability of a dendritic cell, comprising removing an immature dendritic cell from the animal, pulsing the dendritic cell with isolated TRANCE comprising an amino acid sequence of SEQ ID NO:4, conservative variants thereof, fragments thereof, or analogs or derivatives thereof, pulsing the dendritic cell with an isolated protein which is a member of the TNF superfamily of proteins, such that the pulsed dendritic cell comprises an increased viability relative to a control dendritic cell not pulsed with isolated TRANCE and the isolated protein.

64. (Withdrawn) The method of claim 63, wherein the pulsing steps occur simultaneously.

65. (Withdrawn) The method of claim 63, wherein the isolated protein which is a member of the TNF superfamily comprises CD40L and TNF- α .

66. (Withdrawn) A method for increasing viability of a dendritic cell of an animal in vivo, comprising: removing an immature dendritic cell from the animal; pulsing the immature dendritic cell with an isolated TRANCE comprising an amino acid sequence of SEQ ID NO:2, conservative variants thereof, fragments thereof, or analogs or derivatives thereof; inducing the immature dendritic cell to mature; and reintroducing the mature dendritic cell into the animal.

67. (Withdrawn) The method of claim 66, further comprising the step of washing the dendritic cell before reintroducing the dendritic cell into the animal.

68. (Withdrawn) A method for increasing viability of a dendritic cell of an animal in vivo, comprising: Removing an immature dendritic cell from the animal; pulsing the immature dendritic cell with an isolated TRANCE comprising an amino acid sequence of SEQ ID NO:4, conservative variants thereof, fragments thereof, or analogs or derivatives thereof; inducing the immature dendritic cell to mature; and reintroducing the mature dendritic cell into the animal.

69. (Withdrawn) The method of claim 68, further comprising the step of washing

the dendritic cell before reintroducing the dendritic cell into the animal.

70. (Withdrawn) A method for increasing immune response in an animal towards an antigen, comprising the steps of: Removing removing an immature dendritic cell from the animal; pulsing the immature dendritic cell with an isolated TRANCE comprising an amino acid sequence of SEQ ID NO:2, conservative variants thereof, fragments thereof, or analogs or derivatives thereof; pulsing the immature dendritic cell with the antigen; inducing the immature dendritic cell to mature; and reintroducing the mature dendritic cell into the animal.

71. (Withdrawn) The method of claim 70, further comprising the step of washing the dendritic cell before reintroducing the dendritic cell into the animal.

72. (Withdrawn) The method of claim 70, wherein the antigen comprises: b) a pathogen, or a fragment thereof; c) a virus, or a fragment thereof; and d) a tumor, or a fragment thereof.

73. (Withdrawn) A method for increasing immune response in an animal towards an antigen, comprising the steps of: removing an immature dendritic cell from the animal; pulsing the immature dendritic cell with an isolated TRANCE comprising an amino acid sequence of SEQ ID NO:4, conservative variants thereof, fragments thereof, or analogs or derivatives thereof; pulsing the immature dendritic cell with the antigen; inducing the immature dendritic cell to mature; and reintroducing the immature dendritic cell into the animal.

74. (Withdrawn) The method of claim 73, further comprising the step of washing the dendritic cell before reintroducing the dendritic cell into the animal.

75. (Withdrawn) The method of claim 73, wherein the antigen comprises: a) a pathogen, or a fragment thereof; b) a virus, or a fragment thereof, and c) a tumor, or a fragment thereof.

76. (Withdrawn) The method of claim 73, wherein the pulsing steps occur simultaneously.

77. (Withdrawn) A method for increasing immune response in an animal towards an antigen, comprising the steps of: Removing an immature dendritic cell from the animal; pulsing the immature dendritic cell with an isolated TRANCE comprising an amino acid sequence of SEQ ID NO:2, conservative variants thereof, fragments thereof, or analogs or derivatives thereof; pulsing the immature dendritic cell with an isolated protein of the TNF superfamily; pulsing the immature dendritic cell with the antigen; Inducing the immature dendritic cell to mature; and reintroducing the dendritic cell into the animal.

78. (Withdrawn) The method of claim 77, further comprising the step of washing the dendritic cell before reintroducing the dendritic cell into the animal.

79. (Withdrawn) The method of claim 77, wherein the antigen comprises: a) a pathogen, or a fragment thereof; b) a virus, or a fragment thereof; and c) a tumor, or a fragment thereof.

80. (Withdrawn) The method of claim 77, wherein the isolated protein of the TNF superfamily comprises CD40L or TNF- α .

81. (Withdrawn) The method of claim 77, wherein the steps of pulsing the dendritic cell are performed simultaneously.

82. (Withdrawn) A method for increasing immune response in an animal towards an antigen, comprising the steps of: Removing an immature dendritic cell from the animal; pulsing the immature dendritic cell with an isolated TRANCE comprising an amino acid sequence of SEQ ID NO:4, conservative variants thereof, fragments thereof, or analogs or derivatives thereof; pulsing the immature dendritic cell with an isolated protein of the TNF superfamily; pulsing immature the dendritic cell with the antigen; Inducing the immature dendritic cell to mature; and reintroducing the dendritic cell into the animal.

83. (Withdrawn) The method of claim 82, further comprising the step of washing the dendritic cell before reintroducing the dendritic cell into the animal.

84. (Withdrawn) The method of claim 82, wherein the antigen comprises: a) a pathogen, or a fragment thereof; b) a virus, or a fragment thereof; and c) a tumor, or a fragment thereof.

85. (Withdrawn) The method of claim 82, wherein the isolated protein of the TNF superfamily comprises CD40L or TNF- α .

86. (Withdrawn) The method of claim 82, wherein the steps of pulsing the dendritic cell are performed simultaneously.